MEDICAL RESEARCH FORUM

Arranged by the Committee on Medical Education

JANUARY 26, 1955

ABSTRACTS

Cirrhosis of the Liver with Portal Hypertension in Cystic Fibrosis of the Pancreas

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It is known that some infants and older children with cystic fibrosis of the pancreas are found at autopsy to have scattered through the liver small areas of biliary cirrhosis. Also, occasional patients are found at postmortem to have extensive hepatic cirrhotic changes. It has not been realized, however, that the localized liver lesions which are not clinically manifest may progress to widespread cirrhosis of the liver with hepatosplenomegaly and portal hypertension.

The first lesion is a biliary cirrhosis with concretions, focal tissue destruction and no diffuse architectural remodeling. This may be limited to a few areas or may become extensive. Even in the latter case the scattered character of the lesions is such that even though a significant amount of parenchyma is involved, there are no clinical or laboratory symptoms. In particular, there is no jaundice. At autopsy in such patients the liver appears grossly and deeply lobulated, real hepar lobatum. The microscopic picture is striking and distinctive. There is diffuse portal cirrhosis with disorganization characterized by: biliary proliferation, inflammatory reaction, "concretions" of amorphous eosinophilic material plugging the bile ductules and absence of bile stasis. The nature of the concretions is not clear, but morphologically and histochemically they resemble those in the pancreas which have been thought to be formed by inspissated secretions.

As it progresses, the cirrhotic process leads to considerable distortion in the architecture of the liver parenchyma and in some cases hepatic fibrosis becomes so diffuse as to render difficult on biopsy the distinction from the late stage of other types of cirrhosis. The remodeling of the liver is such that portal hypertension eventually develops. It is at this stage that the condition becomes clinically manifest with the appearance of hepatosplenomegaly and later hypersplenism, gastrointestinal bleeding, ascites or a combination of the three. The liver chemistries are often abnormal at this time. Patients may require surgery in an attempt to relieve excessive pressure in the portal system by means of a splenorenal or portocaval shunt.

Biliary cirrhosis with concretions of the type described has been present in 11 per cent of the sixty-three patients with cystic fibrosis of the pancreas that came to autopsy at Babies Hospital. Another seven have had cirrhosis with portal hypertension or about 3 per cent of the 286 cystics seen to date. All of these seven patients had pulmonary

and sweat gland involvement. In five of the cases complete exocrine deficiency of the pancreas was present, but the remaining two had normal pancreatic function. Three were operated and had a shunting procedure performed by Arthur H. Blakemore.

It should be stressed, therefore, that the hepatic area is not infrequently involved in cystic fibrosis of the pancreas. Some of such patients go on to manifest cirrhosis of the liver with portal hypertension, accounting for about one-third of pediatric cases with this clinical picture. From the diagnostic standpoint the combination of abnormally high sweat electrolytes and of chronic pulmonary disease should lead to the suspicion of cystic fibrosis even in the absence of pancreatic deficiency.

Thorazine-Rauwolfia Serpentina Combination in the Treatment of Essential Hypertension*

(Preliminary Report)

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Essential hypertension is treated medically, today, with more than two dozen preparations, most of which cause disturbing side effects or fail to produce the desired response. This preliminary report is concerned with the results of treatment carried out over a period of one year, on one hundred patients, using a combination of Thorazine and Rauwolfia serpentina. Thorazine is a non-barbiturate central depressant agent;[1-10] Rauwolfia serpentina acts directly on the hypothalamus and inhibits the sympathetic system. The latter, has been used quite extensively for the treatment of essential hypertension.[11, 12]

One hundred patients (non-hospitalized) were placed on varying combinations of Thorazine and Rauwolfia serpentina. The optimal dosage was found to be 15.0 mg. of Thorazine and 50.0 mg. of Rauwolfia serpentina, given orally three times daily. Clinical deportment, blood pressure readings, renal function, eye ground examinations, heart size and other usually accepted criteria were studied; patients were observed at varying intervals ranging from daily to weekly.

Preliminary study of the results suggest that the combination of Thorazine-Rauwolfia serpentina is a potent anti-hypertensive agent, with no adverse effects; 85 per cent of the patients with mild hypertension, 70 per cent with moderate hypertension and 60 per cent with severe hypertension were benefited by the use of this combination. Thorazine, used alone, depressed blood pressure for approximately two weeks, after which the blood pressure reverted to its base line. Rauwolfia serpentina, alone, is effectual in the management of mild hypertension. Its action appears to be synergistically enhanced and prolonged by combining it with Thorazine.

This preliminary report describes a new therapeutic combination which gives promise in the management of essential hypertension, without the accompanying adverse and/or toxic effects of the presently used preparations. The site of action of this combination in the brain is the subject of present investigation.

* Thorazine—Brand of Chlorpromazine, Smith, Kline & French Laboratories.

TABLE I.—SUMMARY OF RESULTS

Preparation	*Response*	*Duration*	*Remarks*
PLACEBO	Fair	4-10 Days	No significant drop in BP
THORAZINE (15.0 mg. TID)	Poor	10-14 Days	BP drop rarely persists more than 14 days
RAUWOLFIA (50.0 mg. TID) (Whole root)	Good in mild and controlled cases	10-14 day lag; persists during therapy	Good therapy in mild cases; few side effects with this dosage
Combination of: THORAZINE (15.0 mg.) RAUWOLFIA (50.0 mg.) TID	Mild cases: Excellent Mod. cases: Excellent Sev. cases: Good	during therapy	Synergistic enhancement: no significant side effects; smaller doses possible with persistence of therapy

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Thyroidal Uptake and Plasma Level of Radioactive Iodine in the Diagnosis of Untreated Hyperthyroidism

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The diagnosis of hyperthyroidism in previously untreated patients can often be made quite readily by consideration of the history, physical findings, and easily available laboratory tests. Frequently, however, hyperthyroidism is far from obvious, and conversely may be absent despite the display of some of the characteristic signs and symptoms. Since the introduction by Hertz in 1938 of the use of radioactive iodine for the diagnosis of thyroid disorders, various improvements in technique have been developed. At the present time the uptake of radioactive iodine by the thyroid gland is measured twenty-four hours after a suitable tracer dose. In 1950 we pointed out the diagnostic value of determinations of the level of protein-bound I-131 in the plasma at seventy-two hours after the tracer dose. The purpose of this paper is to present the results of these two tests in a series of about 500 individuals of whom about 100 were considered undoubtedly hyperthyroid and the balance euthyroid. None of these had been subjected to surgery or had received therapeutic doses of I-131. Also excluded were all patients receiving anti-thyroid drugs, iodides or thyroid extract, cortisone or ACTH, or who had been subject to diagnostic procedures involving the use of radio-opaque iodine-containing compounds.

Results: The results of the PBI-131* and of the uptake measurements have been studied graphically by means of frequency distribution curves. These indicate clearly the very considerable overlap in uptake measurements between normal individuals and hyperthyroid patients. The overlap is much smaller in the figure showing plasma levels of PBI-131.

Statistical analysis of the results of these two tests when studied for the likelihood of error in diagnosis indicates that at the level of PBI-121 of 0.26 per cent of the administered dose per liter of plasma the total errors in 500 cases were 1.6 per cent. Similar treatment of the uptake data indicates that the same accuracy can be obtained only by accepting a doubtful range between 42 and 69 per cent and calling only those below 42 per cent normal and those above 69 per cent hyperthyroid. This leaves 27 per cent of the patients undiagnosed by this technique. When uptakes within this range are encountered, additional diagnostic tests are necessary, such as the PBI-131 at seventy-two hours.

Summary and Conclusions: Various methods for the diagnosis of hyperthyroidism have been reviewed. The value of studies with radioactive iodine, by means of both twenty-four hour thyroidal uptake and seventy-two to ninety-six hour plasma levels, has been assayed. A reliable method for determination of the plasma level with the aid of the well-type crystal scintillation counter has been described. Evidence has been presented which indicates that twenty-four hour uptake measurements between 42 and 69 per cent must be considered doubtful if an over-all accuracy equal to that of the blood level method is desired. Seventy-two to ninety-six hour plasma levels above 0.26 per cent of the administered dose per liter of plasma may be considered hyperthyroid in untreated individuals. Levels below 0.26 per cent are usually found only in euthyroid individuals.

* PBI-131 is defined as per cent of administered dose of I-131 bound to the proteins per liter of plasma, after 72 hours.

Occurrence of Myeloid Leukemia in Patients with Metastatic Thyroid Carcinoma Following Prolonged Massive Radioiodine Therapy

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At Montefiore Hospital two cases of subacute leukemia have occurred in a series of sixteen patients with metastatic thyroid carcinoma intensively treated with radioiodine. This series covers the period from 1940 to 1954. Eleven of the group are dead. The radioiodine received by these patients ranged from 195 mc. to 2290 mc. over a six-month to nine-year time interval. The five patients still living have been treated with 275 to 1030 mc. I^{131} over a period of from one to six years.

Patient J.F., a white male of sixty-two, was treated for four years. He received a total of 1455 mc. I^{131}, which delivered a blood radiation dose of about 600 rad. Five months before death, he developed anemia without leukopenia. Two months later episodes of "virus pneumonia" began to occur with persistent low-grade fever. His cervical lymph nodes became enlarged and blood began to appear in the stools. During the last month of his life, the peripheral blood showed anemia, scarcity of blood platelets and presence of myelocytes and myeloblasts. He died in 1951 with a clinical picture of subacute myeloid leukemia. Postmortem studies demonstrated, among other findings, myelogenous leukemia involving bone marrow, spleen, liver and lymph nodes; also anaplastic carcinoma of thyroid metastases to cervical lymph nodes, skull, spine and lungs.

Patient B.L., a white female of sixty-six, was treated for about five years. She received a total of 1600 mc. I^{131}. The patient had transient leukopenias since the beginning of radioiodine treatment. The leukopenia became more marked in the last three years, and was accompanied by anemia. Since June 1953 her differential count began to show "abnormal forms" and high "lymphocyte" counts. In September 1954 the WBC count began to rise rapidly with a high proportion of myelocytes and myeloblasts. Both clinically and hematologically she exhibited the picture of acute myeloid leukemia. At autopsy, among other findings, there was evidence of leukemic infiltration of the spleen, liver and bone marrow.

We do not claim that a causal relationship between radioiodine therapy and leukemia is definitely established by these results. However, the occurrence of these two cases in a series of sixteen patients makes the presumptive evidence strong for the correlation. Moreover, the experimental production of leukemia in animals by radiation, the frequent occurrence of leukemia among radiologists as compared to other physicians, and the high incidence of chronic myelogenous leukemia among the survivors of the Hiroshima and Nagasaki atomic explosions—all these facts corroborate the evidence for a relationship between massive radioiodine therapy and the development of leukemia.

There is a striking absence of leukemia among the thousands of hyperthyroid patients treated with radioiodine during the last fourteen years. For hyperthyroid patients the radiation administered is a small fraction, the order of 1/100, of that given to patients treated for metastatic thyroid carcinoma. The time of exposure is also shorter. This would seem to indicate that the minimum necessary requirements for the development of leukemia in susceptible individuals are either high levels of radiation delivered over a short interval of time or radiations of low intensities extending over a protracted period.

In the two cases we are now reporting the factors of both radiation dose and time of exposure were large.

* Deceased, January 2, 1955.

*The Significance of the Depression of Individual Complement Components for the Differential Diagnosis of Renal Diseases**

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Serum complement values reflect an activity rather than the presence of a uniform substance. There are at least four components of complement (C'1, C'2, C'3 and C'4) which can be quantitatively estimated in the serum of human beings and experimental animals. Lowering of serum complement levels is usually due to the lowering of one of the components which becomes the limiting factor of the total activity. Typical immune precipitates remove from serum mostly component C'4 and, to a lesser extent, C'2, while the levels of components C'1 and C'3 remain unaltered.

When isolated rat kidneys are perfused with fresh rat serum and nephrotoxic antiratkidney rabbit sera are added in small amounts, the complement level rapidly falls after passage through the kidney. These nephrotoxic sera were shown to produce in the intact animal a nephrotic syndrome in a high percentage of cases. When the perfusing sera were analyzed for individual complement components a lowering of component C'2 and, to a lesser extent, of C'4 was found. An identical pattern of removal of complement components was found in the sera of rabbits in which experimental nephritis was produced by the injection of nephrotoxic duck sera.

Ten cases of acute human glomerulonephritis all showed a marked lowering of complement activity. When these sera were analyzed for individual complement components, component C'4 was always found to be the limiting factor. A similar lowering of complement activity was found in four cases of lupus erythematosus disseminatus with an identical pattern of complement components.

When sera of ten patients with the nephrotic syndrome were studied in a similar way, all were found to have lowered complement activity. When they were analyzed, however, for individual complement components, it was found that in all of them C'2 was the limiting factor while C'4 occasionally was lowered but to a lesser degree. This was the case irrespective of whether or not an underlying glomerulonephritis could be demonstrated.

One is thus able to decide from a serum complement determination whether active disease is present and in addition, by determining individual complement components, whether one is dealing with an acute glomerulonephritis or a nephrotic syndrome.

* Supported by Research Grant A-302 (R) of the National Institute of Arthritis and Metabolic Diseases of the National Institutes of Health, Public Health Service, Bethesda, Maryland.

Clinical Experience with the Injection of Streptokinase Intramuscularly in the Treatment of Infections and Edema

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The ability of trypsin to influence the inflammatory reaction has been demonstrated. This phenomenon may be mediated by plasmin. It was of interest to determine whether an anti-inflammatory effect or an anti-edema effect could be produced by the intramuscular administration of streptokinase, a known activator of plasminogen. The features of the inflammatory reaction which localizes infection are barriers to the effective action of the humoral, chemotherapeutic and antibiotic agents. The removal of any of these factors should aid bodily defenses and drugs to attack bacteria more successfully. Observations in patients with infections and edema indicate that profound changes in reversing these states can be effected by the intramuscular administration of streptokinase. The mechanics of the action are at present presumptions and not proven by microscopic examinations or chemical analyses. The anti-inflammatory and anti-edema effects of streptokinase were investigated in three ways. In the first, streptokinase was added to the blood plasma of the patient. In the second, streptokinase was given intramuscularly. In the third, streptokinase was added to an aqueous solution of polyvinyl pyrollidone in the hope that the latter would act as a retarding agent in the absorption of the former. The results in sixty-eight patients, a small number of whom were controls, are analyzed. The results in general have been excellent. Treatment with streptokinase given intramuscularly must be accompanied by the administration of a chemotherapeutic or an antibiotic agent. The use of streptokinase given intramuscularly is not a substitute for sound surgical treatment. Further investigation in the use of streptokinase given intramuscularly is indicated.

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Debridement of Burn Slough by Peptidases Recovered From Clostridium Histolyticus

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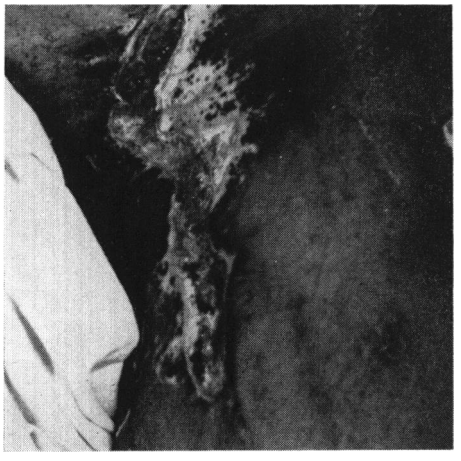
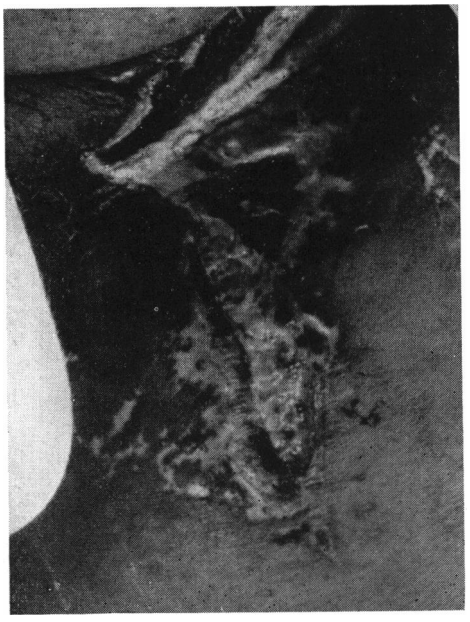
Three enzymes have been recovered from the fermentation of Cl. histolyticum by a second ammonium sulfate fractionation. These are 1) a proteinase obtained at a 17-20 per cent concentration of ammonium sulfate, 2) a collagenase obtained at 23-29 per cent concentration and 3) peptidases obtained at 30-35 per cent concentration. Previously, two fractions, a collagenase and proteinase were isolated, the first by a single ammonium sulfate fractionation and the second by methanol precipitation. Both enzymes were shown to be capable of separating burn slough. The proteinase was found to attack denatured collagen while the collagenase liquefied undenatured collagen. The addition of a small amount of the collagenase to the proteinase aided the proteinase in removing slough. This result was not unexpected because burned skin consists of both undenatured and denatured collagen.



Multiple eschars in left groin. Most caudal eschar is beginning to separate but the ones at the top are still intact and very adherent.

That the peptidase obtained by the new method of separation was also capable of removing burn slough came as a complete surprise, however. Peptidases are only capable of breaking down peptides into amino acids. For this reason the peptidase fraction was not even tested against burn buttons until after the more potent proteinase obtained by the second fractionation method was thoroughly tested. Then it was discovered to be a very active agent. As little as 0.25 mg. per cc. removed burn slough within twenty-four hours, when 1 cc. was injected under a burn 1 cm. in diameter. This occurred without causing hemorrhage in at least sixteen different rabbits, and a healthy base was left behind that quickly granulated. When injected intracutaneously in normal skin, a slight redness developed for twenty-four hours but no ulceration occurred. Mice have been given 0.2 cc. intravenously in doses from 0.12 to 2.0 mg. per cc. to test its general toxicity. At the highest level, the mice receiving 2.0 mg. per cc. were sick for twenty-four hours with rapid respiration and were semi-stuporous for a while but then recovered. Those given 1.0 mg. per cc. were unaffected. The peptidase of the Cl. histolyticum fermentation does not digest burn slough in vitro. Hence it must be assumed that it activates a tissue enzyme.

0.5 mg. per cc. has been used to treat a sloughing lesion on the foot of a diabetic; 10 cc. were used to wet the dressing and left for twenty-four hours. No ill effects



Three days later. Entire slough removed. One section with each injection. First, the most caudal, then the intermediate and lastly, the most cephalad where there is a deep defect in the subcutaneous tissue. All three promptly healed.

were encountered, the patient's temperature did not rise nor were there any changes in his urine. Symptomatically, the foot felt better according to the patient's own volunteered statement. On inspection, most of the slough was removed and there were pink healthy granulations everywhere.

Another patient has received injection into slough that occurred in the left groin following a gland dissection. The first dose given was 4 cc. and the second dose 10 cc. No complications resulted from either amount. The first injection resulted in removal of part of the treated slough and distinct liquefaction without separation of the rest. The second injection resulted in complete separation of the treated portion. Pyocyaneus was present in this hard slough that was deeply adherent and attached, although it was twenty days old.

Peptidases have a wide distribution in the human body. Red blood cells, normal skin and granulation tissues contain peptidases. Peptidases are also found in yeast fermentations and in erepsin secreted in the small intestines. There are at least twelve peptides that can be attacked by them. Certain peptidases are capable of attacking only single peptides, while others attack combinations. Therefore they are spoken of as di, tri and carboxy peptidases. The peptidase found in erepsin does not remove burn slough hence the peptidase obtained from the fractionation of the fermentation of Cl. histolyticum must be a very specific peptidase.

Our future experimental approach is to characterize this peptidase as accurately as possible by testing it against numerous peptides, recognized by paper chromotography. As soon as the nature of this particular peptidase is determined, an attempt will be made to find a plentiful, cheaper source.

Pathological sections made of the burn slough treated with peptidase will be compared to the leukocytic reaction occurring about the untreated burn slough. Histochemistry will be employed to determine whether differences can be demonstrated.

Clinical Evaluation of the Tobacco Ballistocardiogram

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Clinical decision as to the detrimental cardiovascular effects of smoking in individual patients has rested heretofore on the personal opinion and prejudices of the examining physician. Electrocardiographic alterations after smoking have proved to be of decisive value only rarely. Conversely, the ballistocardiographic response to smoking appears to be a sensitive objective index in this regard.

The effects of smoking on the direct ballistocardiogram were investigated in one hundred unselected private patients. Complete cardiac survey was made including electrocardiogram, fluoroscopy and/or chest roentgenogram, ballistocardiogram and exercise tolerance test. The ballistocardiogram was recorded in the basal state after overnight abstinence from smoking. Using the Dual ballistocardiograph, direct Dock-type tracings were taken in slight held inspiration, deep inspiration and deep expiration. Both photoelectric (displacement) and electromagnetic (velocity) records were taken in all cases. The patients were then asked to smoke at their customary rate, usually two standard cigarettes. Ballistocardiograms were then recorded again immediately after cessation of smoking.

For purposes of analysis, the cases were divided into two groups: first, normal control patients with no clinical evidence of organic heart disease and second, patients with angina pectoris due to arteriosclerotic coronary artery disease. The results disclosed that in sixty-six non-cardiacs the tobacco ballistocardiogram was abnormal in seventeen, borderline in six and normal in forty-three. In thirty-four cardiacs with angina pectoris the tobacco ballistocardiogram was positive in eighteen, borderline in one and negative in fifteen. Thus the procedure was abnormal in 26 per cent of noncardiac patients as against 53 per cent of the cardiac group.

In several instances in this investigation, various commercially available filter cigarettes were tested as well as the standard types. The use of filters definitely affected the tobacco ballistocardiographic tests, in that the alterations noted previously with standard cigarettes were either minimized or abolished in many cases. In a few cases with abnormal tobacco ballistocardiograms, skin tests for tobacco allergy were negative.

Follow-up studies of sixteen patients who discontinued smoking after positive tests revealed uniform clinical improvement with complete cessation of chest pain in seven. The tobacco ballistocardiogram is presented as a valuable and objective screening test for routine application in clinical cardiac practice.